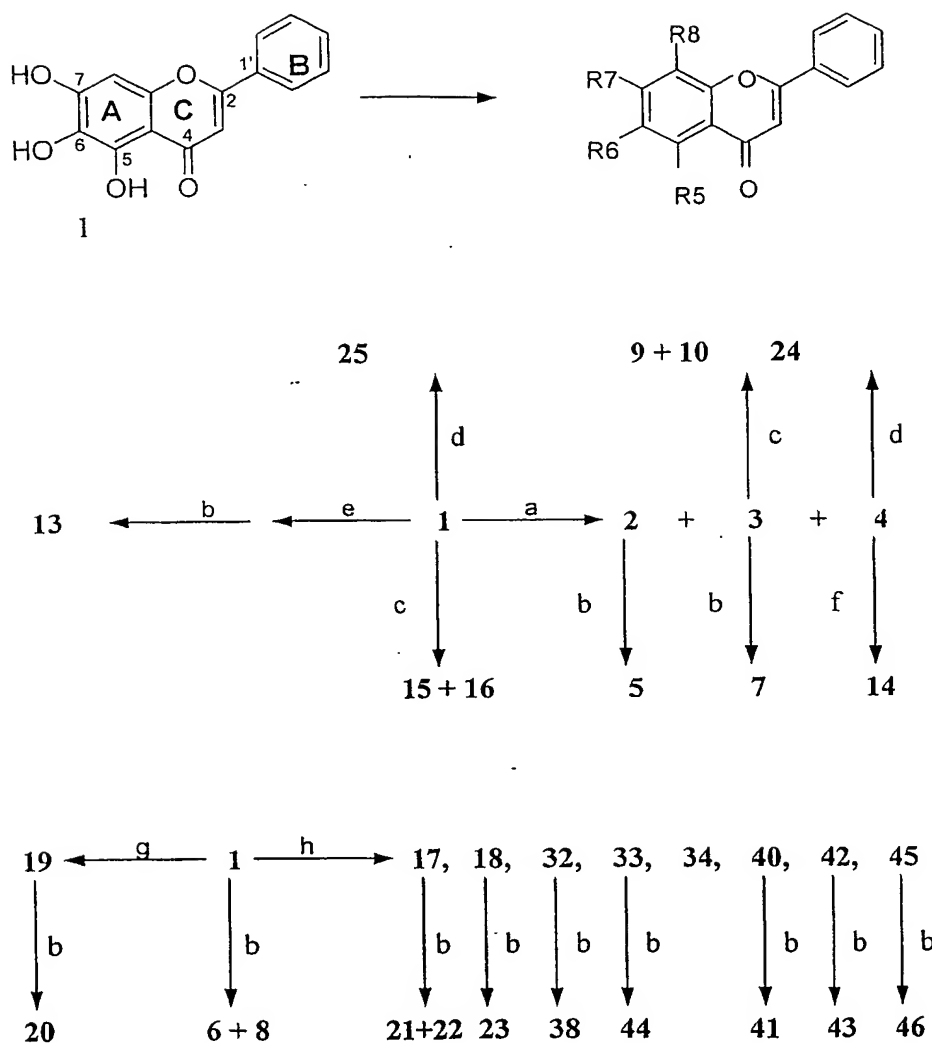


FIGURE 1 Scheme 1^a

^a Reagents and conditions: (a) Ac_2O , pyridine, rt; (b) TMSCHN_2 , $\text{THF}:\text{MeOH}$ (2:1), rt; (c) K_2CO_3 , BnBr , acetone, reflux; (d) NBS , THF , *conc* H_2SO_4 , rt; (e) Ph_2CCl_2 , 170 °C; (f) K_2CO_3 , KI , BnBr , acetone, reflux; (g) Cs_2CO_3 , BrCH_2Cl , DMF , 50 °C; (h) K_2CO_3 , $\text{CH}_3(\text{CH}_2)_n\text{X}$ ($\text{X}=\text{I}$ or Br , $n=1$ for 32, 33, $n=2$ for 17, 18, $n=3$ for 45, $n=4$ for 40, $n=5$ for 42, $n=7$ for 34), acetone, reflux.

FIGURE 2

Table 1. Anti-P-gp activity and cytotoxicity of acetylated baicalein compounds.

compd	functional group				c log P ^a	anti-P-gp activity ^b		cytotoxicity IC ₅₀ (μM)	
	R5	R6	R7	R8		EC ₅₀ (μM) ^d	A _{max} ^c	KB	KB/MDR
control							0.5±0.1 ^f		
CSA					2.9	1.2±0.3	3.5±0.3	0.6±0.2	1.5±0.7
VRM					4.5	14±1.2	2.2±0.1	19.6±2.7	51.7±4.7
1	OH	OH	OH	H	3.0	41±5.1	1.7±0.1	62.3±3.7	87.1±3.6
2	OH	OAc	OH	H	2.5	11±2.1	3.1±0.2	10.5±1.4	61.6±4.8
3	OH	OAc	OAc	H	2.4	9.7±1.8	2.6±0.1	12.7±2.3	69.3±6.4
4	OAc	OAc	OAc	H	1.2	6.8±0.7	3.0±0.2	14.5±2.1	57.2±7.3
7	OMe	OAc	OAc	H	1.7	12.3±1.5	2.9±0.1	> 100	>100
5	OMe	OAc	OMe	H	2.3	11.5±1.1	2.4±0.1	85.5±8.5	>100
24	OH	OAc	OAc	Br	3.1	15±3.1	1.8±0.3	12.4±2.7	16.2±2.3
25	OH	OH	OH	Br	3.7	15±2.9	1.8±0.2	14.1±1.4	18.7±3.1

Ac = acetyl and Me = methyl.

FIGURE 3

Table 2. Anti-P-gp activity and cytotoxicity of benzylated baicalein compounds.

compd	functional group				c log P	anti-P-gp activity ^b		cytotoxicity IC ₅₀ (μ M) ^e	
	R5	R6	R7	R8		EC ₅₀ (μ M) ^d	A _{max} ^c	KB	KB/MDR
control							0.5 \pm 0.1 ^f		
CSA					2.9	1.2 \pm 0.3	3.5 \pm 0.3	0.6 \pm 0.2	1.5 \pm 0.7
VRM					4.5	14 \pm 1.2	2.2 \pm 0.1	19.6 \pm 2.7	51.7 \pm 4.7
1	OH	OH	OH	H	3.0	41 \pm 5.1	1.7 \pm 0.1	62.3 \pm 3.7	87.1 \pm 3.6
9	OBn	OAc	OAc	H	3.5	3.7 \pm 0.2	3.6 \pm 0.2	11.3 \pm 1.7	12.2 \pm 1.1
10	OH	OBn	OAc	H	4.7	2.4 \pm 0.1	2.8 \pm 0.1	16.3 \pm 2.1	18.3 \pm 2.3
14	OAc	OAc	OBn	H	3.5	1.1 \pm 0.1	3.4 \pm 0.2	13.4 \pm 2.4	13.7 \pm 2.1
15	OH	OBn	OH	H	4.8	1.8 \pm 0.1	3.7 \pm 0.2	4.3 \pm 1.6	3.2 \pm 1.2
16	OH	OBn	OBn	H	7.1	70 \pm 5.4	1.1 \pm 0.1	> 100	>100
13	OMe	OCP _{h2} O		H	6.7	11.5 \pm 2.2	1.9 \pm 0.1	60.5 \pm 5.5	40.6 \pm 3.4

Bn = benzyl, Me = methyl, and Ph = phenyl.

FIGURE 4

Table 3. Anti-P-gp activity and cytotoxicity of alkylated baicalein compounds.

compd	functional group				c log P ^a	anti-P-gp activity ^b		cytotoxicity IC ₅₀ (μM)	
	R5	R6	R7	R8		EC ₅₀ (μM) ^d	A _{max} ^c	KB	KB/MDR
control							0.5±0.1 ^f		
CSA					2.9	1.2±0.3	3.5±0.3	0.6±0.2	1.5±0.7
VRM					4.5	14±1.2	2.2±0.1	19.6±2.7	51.7±4.7
1	OH	OH	OH	H	3.0	41±5.1	1.7±0.1	62.3±3.7	87.1±3.6
8	OH	OMe	OMe	H	3.5	4.6±1.1	3.4±0.3	> 100	> 100
6	OMe	OMe	OMe	H	2.9	5.5±0.4	2.7±0.2	85.9±7.8	57.9±5.9
19	OH	OCH ₃ O		H	3.7	6.5±1.3	1.2±0.1	> 100	> 100
20	OMe	OCH ₃ O		H	3.1	4.4±2.1	1.5±0.1	> 100	> 100
32	OH	OEt	OH	H	3.6	2.3±0.3	3.5±0.3	24.6±3.5	17.5±5.6
38	OH	OEt	OMe	H	4.1	1.5±0.3	2.3±0.2	> 100	> 100
33	OH	OEt	OEt	H	4.6	1.8±0.2	4.9±0.2	> 100	> 100
44	OMe	OEt	OEt	H	3.9	1.1±0.1	4.2±1.1	81.7±7.8	79.2±5.8
17	OH	OPr	OH	H	4.1	2±0.7	4.7±0.1	58.9±6.3	> 100
21	OH	OPr	OMe	H	4.6	1.2±0.4	4.6±0.1	> 100	> 100
22	OMe	OPr	OMe	H	3.9	1.7±0.1	4.6±0.1	> 100	> 100
18	OH	OPr	OPr	H	5.6	1.4±0.4	5.0±0.2	> 100	> 100
23	OMe	OPr	OPr	H	5.0	0.9±0.1	5.2±0.1	86.4±6.3	93.7±2.2
45	OH	OC ₄ H ₉	OC ₄ H ₉	H	6.7	1.5±0.3	3.2±0.1	> 100	> 100
46	OMe	OC ₄ H ₉	OC ₄ H ₉	H	6.1	1.6±0.2	4.4±0.1	> 100	> 100
40	OH	OC ₅ H ₁₁	OC ₅ H ₁₁	H	7.8	1.8±0.1	1.1±0.1	> 100	> 100
41	OMe	OC ₅ H ₁₁	OC ₅ H ₁₁	H	7.1	1.5±0.1	3.2±0.1	75.4±6.4	82.6±8.4
42	OH	OC ₆ H ₁₃	OC ₆ H ₁₃	H	8.8	1±0.1	1.0±0.1	> 100	> 100
43	OMe	OC ₆ H ₁₃	OC ₆ H ₁₃	H	8.2	1.3±0.2	1.1±0.1	39.1±8.5	44.8±7.9
34	OH	OC ₈ H ₁₇	OC ₈ H ₁₇	H	10.9	7.4±4.1	1.2±0.1	> 100	> 100

Me = methyl, Et = ethyl, Pr = *n*-propyl and Ph = phenyl.